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Natural Progression Model of Cognition and Physical Functioning among People with Mild Cognitive Impairment and Alzheimer's Disease

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Abstract.
Background: Empirical models of the natural history of Alzheimer's disease (AD) may help to evaluate new interventions for AD.
Objective: We aimed to estimate AD-free survival time in people with mild cognitive impairment (MCI) and decline of cognitive and physical function in AD cases.
Methods: Within the Kungsholmen project, 153 incident MCI and 323 incident AD cases (international criteria) were identified during 9 years of follow-up in a cognitively healthy cohort of elderly people aged $\geq$75 at baseline ($n = 1{,}082$). Global cognitive function was assessed with the Mini-Mental State Examination (MMSE), and daily life function was evaluated with the Katz index of activities of daily living (ADL) at each follow-up examination. Data were analyzed using parametric survival analysis and mixed effect models.
Results: Median AD-free survival time of 153 participants with incident MCI was 3.5 years. Among 323 incident AD cases, the cognitive decline was 1.84 MMSE points per year, which was significantly associated with age. Physical functioning declined by 0.38 ADL points per year and was significantly associated with age, education, and MMSE, but not with gender.
Conclusion: Elderly people with MCI may develop AD in approximately 3.5 years. Both cognitive and physical function may decline gradually after AD onset. The empirical models can be used to evaluate long-term disease progression of new interventions for AD.

Keywords: Alzheimer's disease, dementia, disease progression, economic model, mild cognitive impairment

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INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia, is characterized by a gradual onset and a decline of cognition and functional ability to the stages of complete dependence on informal or formal care. When studying the disease, it is therefore important to adopt a long time horizon to capture all disease-related events. Disease modifying treatments are being developed to reduce individual and societal burden, but randomized trials to evaluate such interventions require many years of follow-up to capture their long-term consequences, whereas most trials have employed a short follow-up period [1]. Long-term follow-up requires large investments of resources, and if new interventions emerge during the follow-up period, ethical concerns arise regarding withholding possibly successful treatment for a prolonged period. As an alternative, empirical models can be used to predict long-term consequences by integrating trial outcomes with estimations of natural disease progression [2, 3]. In addition, empirical models are a crucial component of economic decision models [4] that generate evidence for care policy making.

Natural progression models in AD have been developed in several studies [5], mostly among clinical samples or prevalent AD dementia cases. However, disease modifying treatments are supposed to be effective in early (pre-dementia) AD, thus long-term data on the natural course are required to evaluate their effectiveness. Such target populations have not been reflected by previous studies, leaving an urgent need for population-based empirical models that describe the long-term natural progression of the dementia and pre-dementia phases of AD. In the present study, we aimed to build empirical models that estimate (1) the time from incident mild cognitive impairment (MCI) to AD-type dementia and (2) the changes of cognition and function in incident AD dementia cased from a population-based cohort.

METHODS

Study sample

The study sample was derived from the Kungsholmen Project, a population-based cohort study on aging and dementia, which has been fully described elsewhere [6, 7]. Briefly, all registered inhabitants of the Kungsholmen district of Stockholm, Sweden, who were aged $\geq$75 years in October 1987, were initially invited to participate in the project. At baseline, 225 of the 1,810 participants were diagnosed with dementia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) [8], based on a 2-phase survey, and 110 participants refused the extensive evaluations. Of the remaining 1,475 dementia-free persons, 355 with MCI (130 with amnestic MCI (aMCI) and 225 with other cognitive impairment not demented (OCIND)) at baseline and 38 with very low global cognitive status in the absence of a dementia diagnosis (Mini-Mental State Examination (MMSE) [9]<20) were excluded, leaving 1,082 cognitively healthy subjects at baseline.

The participants of the present study were persons with incident MCI and AD-type dementia (either AD or mixed AD & vascular dementia). A 6-year instead of 9-year follow-up for incident MCI was applied to preserve a 3-year exposure term (from 6–9 years) for the progression of MCI to AD dementia as explained below.

During the 9-year follow-up, three sets of clinical examinations were carried out, with average intervals of 3 years. Informed consent was obtained for all participants, with informants providing consent for cognitively impaired persons. The ethics committee at the Karolinska Institutet, Stockholm, approved all phases of the Kungsholmen Project.

Data collection

Data on demographic features (i.e., age, gender, and education) was collected at baseline using standardized protocols [6, 7].

Global cognitive functioning was assessed with the MMSE, and dependency was assessed using the Katz index of activities of daily living (ADL) [10] with scores ranging from 0 (not dependent for ADL) to 6 (fully dependent for ADL).

Diagnosis of dementia

During the follow-up period, a diagnosis of dementia (including both questionable and definite diagnoses) was established by the examining physicians, based on a comprehensive clinical examination and cognitive tests according to the DSM-III-R criteria [11]. The diagnostic criteria applied were equivalent to probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [12], and according to those of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences [13].

Definition of MCI

aMCI was defined according to the original Mayo clinic criteria, and operationalized according to previous research [14, 15], as follows: (1) presence of a memory complaint reported by the participant or by a close informant during the nurse interview; (2) preserved general cognitive functioning, defined as scoring above the minus 1 SD cut-off on age and education adjusted MMSE means; (3) absence of dementia, verified by clinical examination; (4) preserved functional independence defined as no impairment on the Katz ADL scale; (5) presence of objective memory impairment defined as scoring ≥1.5 SD below age- and education-specific means on a verbal memory task of free recall of slowly and rapidly presented words [16]. All cases with global cognitive impairment that did not fulfill criteria for dementia were classified as OCIND and operationalized according to previous research [17] as follows: (1) impaired general cognitive function, defined as scoring 1 SD or more below age and education adjusted means on the MMSE derived from the dementia free population at baseline; and (2) absence of dementia, verified by clinical examination. aMCI and OCIND were mutually exclusive in the present study, therefore a broader category of MCI was created which included cases classified as aMCI or OCIND. The analyses were based on the incident cases of AD detected at the 3-, 6-, or 9-year follow-up measurements and incident cases of MCI detected at the 3- or 6-year follow-up measurement.

Statistical analysis

Survival analysis was applied to estimate the time from incident MCI to AD-type dementia. The effect of age at diagnosis of MCI, gender, education, MMSE, and ADL at diagnosis, and all 2-way interactions was assessed. A stepwise procedure was used (removing interactions with highest p-values first until $p < 0.05$, followed by the predictors).

A mixed model with random subject effects was applied to determine the decline in cognition and ADL over time in incident AD participants. A stepwise procedure was used and predictors were included if the goodness-of-fit statistics −2 log likelihood change and Wald z of the predictor were significant. The following steps were used to determine the final MMSE prediction model: (1) include time, as years after being diagnosed with AD; (2) include a random intercept; (3) determine if time is non-linear by stepwise adding a higher-order polynomial of time (time^2, time^2 + time^{2+n}, etc.); (4) include a random time factor; (5) include gender, age, and education and all 2-way interactions and remove interactions with highest p-values first until $p < 0.05$, followed by predictors.

A similar procedure was used to analyze decline in ADL, and the effect of MMSE was also determined.

The onset of MCI as well as that of AD was assumed to have taken place in the middle of each follow-up interval (each lasting an average of 3 years). This was operationalized by adding a time correction of 1.5 years to all diagnoses. Survival analysis was performed using Stata-12, mixed effect models using SPSS-20.

Table 1
Characteristics of the participants with incident MCI and AD dementia

Characteristics	Incident MCI ($n = 153$)	Incident AD ($n = 323$)
Age in years; mean (SD)	83.4 (4.0)	86.7 (4.1)
Female; %	75%	83%
Years of education; mean (SD)	8.5 (3.0)	8.2 (2.9)
MMSE score; mean (SD)	24.4 (2.1)	19.7 (5.0)
Katz ADL score; mean (SD)	0.4 (0.7)	1.2 (1.7)

RESULTS

Out of 1,082 cognitively healthy participants at baseline, 153 developed MCI (40 aMCI and 113 OCIND) and 323 developed AD during the 6 and 9 years of follow-up, respectively. The mean age at diagnosis of MCI was 83 years, while the mean age at AD diagnosis was 87 years (Table 1). Figure 1 provides an overview of the observed MMSE scores over time in the pre-dementia phase (captured by the survival analysis) and dementia phase (captured by the regression model).

AD-free survival

Among the 153 participants with incident MCI, 48 (31%) developed AD dementia, after a median time of 3.03 years (658 person-years). The incidence rate was 0.073 (95% CI: 0.055 to 0.097). Twenty-nine percent of the participants died during follow-up.

Univariate analysis only showed a significant effect of gender. In the multivariate stepwise analyses, women had a significantly shorter time from MCI to AD than the men (4.2 and 4.6 years, respectively; hazard ratio = 0.38) and none of the 2 way interactions were significant (Table 2). The observed times until 90% and 75% of the MCI cohort were still AD-free were 2.9 and 3.2 years, respectively. The 50% AD-free survival was not reached within the 6-year observation

period. Using the fitted model, the estimated times until 90%, 75%, and 50% of the MCI cohort had survived without developing AD dementia were 2.8, 4.6, and 7.1 years, respectively (see Box 1).

BOX 1

The survivor function is described by equation (1), where *S(t)* is the proportion of AD-free survival, t is time in years, a is the exponent of the survival analysis coefficient estimates, and p is the Weibull shape parameter. This function can be rewritten to estimate the time until a specific proportion (S) of an MCI cohort has progressed to AD dementia, where gender 0 = female and gender 1 = male (equation 2).

$$S(t) = e^{-at^p} \tag{1}$$

$$t = \sqrt[p]{\frac{1\mathrm{n}(S)}{-a}} \tag{2}$$

$$t = \sqrt[2.01]{\frac{1\mathrm{n}(S)}{-e^{-4.06-0.96\ gender_i}}} \tag{3}$$

The course of the MMSE can be summarized by regression formula (4) and the course of ADL by regression formula (5), where r is a random number from a normal distribution to reflect the variance in the random effects, and i is the individual participant.

$$\begin{aligned} MMSE_i = {} & (26.87 \pm \sqrt{2.0 r_i}) - (3.26 \\ & \pm \sqrt{1.86 r_i}) time_i - 0.35(age_i - 75) \\ & + 0.10\, time_i\, (age_i - 75) + e_i \end{aligned} \tag{4}$$

$$\begin{aligned} Katz\ index_i = {} & \left(-0.82 \pm \sqrt{0.71 r_i}\right) \\ & + 0.26\ time_i + 0.26\ (age_i - 75) \\ & + 0.06\ education - 0.02 MMSE \\ & - 0.01 MMSE_i (age_i - 75) \\ & - 0.01 MMSE_i time_i = e_i \end{aligned} \tag{5}$$

Decline in cognitive and physical function

For the 323 participants who developed AD during follow-up, 313 MMSE scores were available at the moment of AD diagnosis, 109 at 3 years after diagnosis, and 28 at 6 years after diagnosis. Forty-nine percent of the participants died during the follow-up.

Figure 2a presents the observed average MMSE scores over time, with 0 representing the moment of AD diagnosis. The univariate analyses showed that age and time (as years after being diagnosed with AD) significantly predicted the MMSE score, with an average rate of decline of −1.84 MMSE points per year. The multivariate model showed that time and age significantly predicted a decrease in MMSE score (Table 3). The interaction between time and age indicates a decreasing rate of decline over time.

For the 323 participants who developed AD during follow-up, 318 Katz ADL scores were available at the moment of AD diagnosis, 109 at 3 years after diagnosis, and 28 at 6 years after diagnosis.

Figure 2b presents the observed average Katz ADL scores over time. The univariate analyses showed that age, education, MMSE, and time significantly predicted the Katz ADL score. The multivariate model showed that time significantly predicted an increase in the Katz ADL score. The interaction between age (measured at each assessment) and MMSE score, as well as that between MMSE score and time after being diagnosed, were significant. Higher education predicted an increase in dependency (Table 3). Box 1 provides an overview of the regression formulas that describe the course of MMSE and ADL.

DISCUSSION

In this long-term population-based prospective study, we found that (1) the median AD dementia free survival time was 3.5 years from the onset of MCI; (2) after the onset of dementia, cognition declined at a mean rate of 1.84 MMSE points per year; (3) Katz ADL dependency score increased at a mean rate of 0.38 points per year; and (4) the above results yielded the mathematical expressions presented in box 1 to describe the natural decline of AD in relation to age, gender, and education.

Our estimates (conversion rate: 7.3%, CI: 5.5–9.7%) are within the confidence intervals of a pooled estimate of the conversion of MCI to AD obtained by averaging several population-based studies of MCI (conversion rate 6.8, CI: 1.9–14.5) [18]. Our punctual estimate of 7.3% for MCI conversion to AD is slightly higher that the pooled punctual estimate of 6.8% calculated by Mitchell et al. [18] and this may be due to the fact that our definition of MCI included cases with global cognitive deterioration (OCIND) who progress faster to AD (aMCI conversion rate was 6.7 and OCIND conversion rate was 7.5). The cumulative conversion rate of 31% suggests that some of the MCI subjects improve

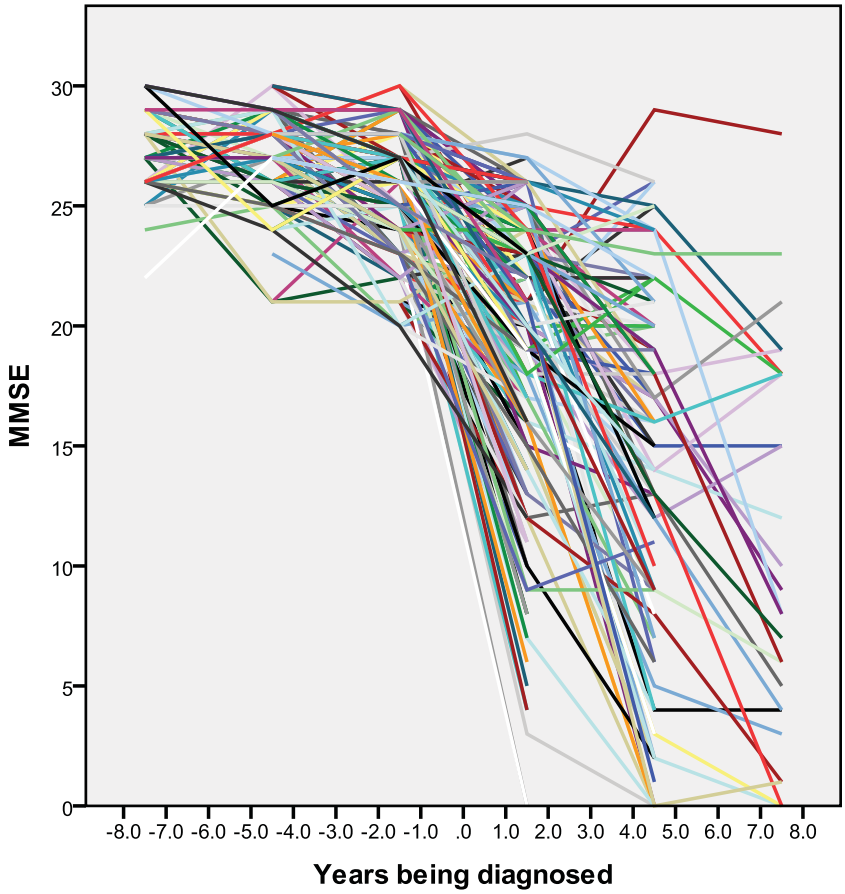

Fig. 1. Course of observed MMSE over time. Each line represents an individual; time = 0 represents the moment when dementia is diagnosed (using a 1.5 year time correction), time = −6 represents 6 years before the diagnosis of dementia.

Table 2
Hazard ratio (95% CI) of AD in the MCI cohort using a parametric survival model with Weibull distribution

Factors	AD Hazard Ratio (95% CI) univariate analyses	AD Hazard Ratio (95% CI) multivariate analysis
Gender (male)	0.38 (0.16 to 0.90)*	0.38 (0.16 to 0.90)*
Age at MCI diagnosis	1.06 (0.99 to 1.14)	
Education	0.94 (0.84 to 1.05)	
MMSE at MCI diagnosis	0.92 (0.80 to 1.07)	
Katz at MCI diagnosis	1.17 (0.72 to 1.88)	

*$p < 0.05$.

and some die before developing dementia [19]. Our decision to use parametric survival analysis requires stricter distributional assumptions, though assuming a specific baseline hazard shape allows the survival function to be used to simulate time to event data for health economic modeling.

A population-based study including 95 incident dementia participants [20, 21] found an average rate of cognitive decline of 1.71 MMSE points per 6 months, whereas we found a lower average rate of decline (1.84 / 2 = 0.92 points per 6 months). The difference could be explained by the inclusion of a higher proportion of moderately severe dementia participants in the Kungsholmen Project, who decline less quickly due to the floor effect of the MMSE. According to the multivariate model using average age, subjects decline by 1.2 MMSE points in the first 6 months after being diagnosed.

Mendiondo et al. [22] and Mohs et al. [23] parameterized the annual rate of cognitive decline and found a U-shaped pattern with low decline rates in mild and severe dementia and a higher decline rate in between. We explored this model, but the results were not significant and could be attributed to the use of a

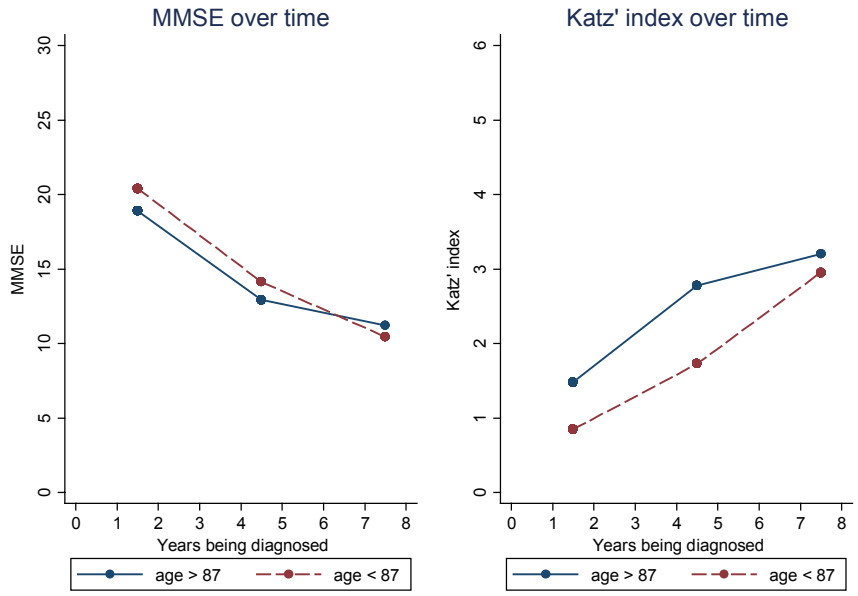

Fig. 2. Course of average observed MMSE over time and the average Katz scores observed over time among incident dementia cases (time = 0 represents the moment dementia is diagnosed; a time correction of 1.5 years was applied; n = xx represent data points available).

Table 3
Regression parameter estimates (95% CI) of univariate and multivariate mixed effects regression model to predict MMSE (to reflect cognition) and Katz score (to reflect ADL), $n = 323$

	Cognition (MMSE)		ADL (Katz score)	
Factors	Univariate	Multivariate	Univariate	Multivariate
Intercept	–	26.87 (24.45 to 29.29	–	−0.82 (−2.30 to 0.65)
Time as years after being diagnosed with dementia	−1.84 (−2.10 to −1.57)*	−3.26 (−4.56 to −1.97)**	0.38 (0.29 to 0.46)**	0.26 (0.08 to 0.44)**
Gender (male)	−1.14 (−2.89 to 0.60)	–	0.33 (−0.15 to 0.81)	–
Age at each assessment moment normalized at 75	−0.41 (−0.57 to −0.26)*	−0.35 (−0.53 to −0.16)**	0.15 (0.11 to 0.20)**	0.26 (0.16 to 0.36)**
Education	−0.05 (−0.29 to 0.19)	–	0.08 (0.02 to 0.14)*	0.06 (0.00 to 0.11)**
MMSE at each assessment moment	–	–	−0.16 (−0.18 to −0.14)**	0.02 (−0.05 to 0.08)
Time squared (2nd order polynomial)	–	–	–	–
Interaction time*age	–	0.10 (0.01 to 0.19)*	–	–
Interaction MMSE*age	–	–	–	−0.01 (−0.01 to −0.00)**
Interaction MMSE*time	–	–	–	−0.01 (−0.02 to −0.00)*
Variance random intercept	–	2.00	–	0.71**
Variance random time effect	–	1.86	–	–
Covariance random intercept and random time effect	–	1.73*	–	–

*$p < 0.05$, **$p < 0.01$.

population-based sample instead of a clinical sample, as the latter probably includes persons with a poorer prognosis because consulting a medical professional is probably initiated by the person's memory complaints. Han et al. [24] reviewed studies largely based on clinical samples of prevalent cases with an average of 2

years of follow-up, and found a mean annual rate of decline of 3.3 MMSE points per year. Our estimates are at the lower bound of their confidence interval. Besides the use of incident community participants, this difference could be explained by the long follow-up time, in which some participants reach the floor level of the MMSE.

Our model for dependency estimated that more years of education increased dependency. This can be explained by higher educated persons having a cognitive reserve which delays receiving a diagnosis of dementia [25]. By the time the diagnosis is established, the disease is probably more severe than in less educated persons, which could mean that higher educated persons have a poorer prognosis. Gender was not found to be significant in the analyses on the demented subjects, which might be explained by limited statistical power, since the sample included about 17% males. In both the MMSE and ADL models, the effect of age indicates a more rapid decline among younger persons. The interaction effects between time and age in the MMSE model runs counter to the effect of time. This suggests a decreasing rate of decline in the later stages of the disease. However, it can also be explained by the bottom level of the MMSE that might be less sensitive in severely demented persons.

The strength of our study was the use of a 6-year follow-up period and the prospective study design. Nevertheless, the study was subject to several limitations. The Kungsholmen project included persons aged 75 and older, which resulted in attrition due to death and refusal. However, this reflects reality, since most demented people are older than 75 [26], and the mixed model with random effects and the survival analysis take missing or censored data into account. Nonetheless, generalization to a younger population should be done with caution, although our finding of a positive relation between age and cognition was also found in clinical samples with a younger age [27]. A second limitation is that the Kungsholmen project started in 1987, when the current cholinesterase inhibitors and memantine treatments that affect cognitive decline were not available. In addition, advances in diagnostics, especially for MCI, might limit the generalization of our findings to the current care standards. Thirdly, the 3-year interval between our measurements may have resulted in a biased estimate of AD dementia free survival in MCI subjects, because a participant may progress to dementia via MCI within an interval without being assessed. Fourthly, the empirical models were not adjusted for comorbidities, as this information was not available to the researchers. Finally, visual comparison between the observed and estimated hazard rates from the survival analysis indicated a difference that can be attributed to the use of 3-year average intervals between assessments. This discrepancy most likely also explains the difference between the observed time until 75% AD free survival (3.2 years) and the estimated survival time derived from the fitted survival model (4.6 years). Furthermore, the 1.5 year correction might limit the precision of the time-to dementia conversion.

The empirical models in Box 1 could be used to simulate the natural disease progression in a cohort and compare this with a scenario where a hypothetical future treatment is available. Such predictions can be integrated with evidence on health care resource usage and quality of life, and enable policy makers to address questions about the potential of new diagnostic or treatment interventions from a cost-effectiveness point of view [28]. Such analyses could provide added value to randomized controlled trials which are limited in terms of follow-up time or the number of scenarios to compare [3]. This should, however, be done with caution, for several reasons. The regression and survival models have not been validated by external datasets, or by predicting the progress of similar patients in current clinical practice. The data available at follow-up was limited, resulting in uncertain predictions. If these results are to be integrated with those from other sources, the populations must be similar. This might represent a difficulty for the evaluation of diagnostic and treatment scenarios, since their evidence is often collected in clinical settings and differs from that derived from a population-based study. This stresses the importance of using sensitivity analysis in decision models to address these issues. Finally, generalizability to other countries is limited because differences in life expectancy might lead to differences in average disease progression rates or the effect of age.

Caution should be used when combining evidence from sources that reflect different populations. Samples recruited within a clinical setting will most likely show more progressive decline, on which age, gender, and education might have different influences. Furthermore, different criteria and subdivisions of MCI have been proposed and modified over time, with different characterizations of cognitive decline (e.g., aMCI specifically reflecting an AD cause and OCIND including a broader range of potential causes [29]). In addition, extrapolation of the results outside the 6-year time frame should also be done with caution.

In conclusion, our results reflect the natural history of AD in the pre-dementia and dementia phases

in terms of cognition and dependency. Since the study was based on community incident cases of MCI and AD dementia, its results can be applied for effectiveness and cost-effectiveness evaluations of interventions in early AD.

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